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### **Patterns of weight change after the diagnosis of type 2 diabetes in Scotland and their relationship with glycaemic control, mortality and cardiovascular outcomes**

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# BMJ Open Patterns of weight change after the diagnosis of type 2 diabetes in Scotland and their relationship with glycaemic control, mortality and cardiovascular outcomes: a retrospective cohort study

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## ABSTRACT

**Objectives:** To determine weight change patterns in Scottish patients 2 years after diagnosis of type 2 diabetes and to examine these in association with medium-term glycaemic, mortality and cardiovascular outcomes.

**Setting:** Using a retrospective cohort design, ethical approval was obtained to link the Scottish diabetes care database to hospital admission and mortality records.

**Participants:** 29 316 overweight/obese patients with incident diabetes diagnosed between 2002 and 2006 were identified with relevant information for  $\geq 2$  years.

**Primary and secondary outcome measures:** Weight records over time provided inpatient weight change and variation and glycated haemoglobin (HbA1c) gave measures of glycaemic control. These characteristics and demographic variables at diagnosis were linked with notifications of death (2–5 years after diagnosis) and cardiovascular events (0–5 year after diagnosis).

**Results:** By 2 years, 36% of patients had lost  $\geq 2.5\%$  of their weight. Increasing age, being female and a higher body mass index at diagnosis were associated with larger proportions of weight lost ( $p < 0.001$ ). Multivariable modelling showed that inadequate glycaemic control at 2 years was associated with being younger at baseline, being male, having lower levels of obesity at diagnosis, gaining weight or being weight stable with weight change variability, and starting antidiabetic medication. While weight change itself was not related to mortality or cardiovascular outcomes, major weight variability was independently associated with poorer survival and increased cardiovascular outcome risks, as was deprivation.

**Conclusions:** Our results suggest that weight loss or being weight stable with little weight variability early after diabetes diagnosis, are associated with better glycaemic control and we identified groups less able to lose weight. With respect to mortality and cardiovascular outcomes, although weight change at 2 years was a weak predictor, major weight variability appeared to be the more relevant factor.

## Strengths and limitations of this study

- This representative study uses the national Scottish diabetes register to study all patients with type 2 diabetes, providing a substantial data set with up to 5 years of follow-up.
- We used novel methods to study the impact of weight change patterns on glycaemic control, and link these to Scottish data for mortality and cardiovascular disease.
- We had sufficient statistical power to identify groups (men, younger patients, those with lower levels of obesity at diagnosis and higher levels of deprivation) who might particularly benefit from structured weight loss interventions.
- There were insufficient numbers of patients on newer antidiabetic medications, such as gliptins and glucagon-like peptide-1 receptor agonists, to analyse their effects.
- The influences of blood pressure and lipid control were not incorporated into the analyses.

## INTRODUCTION

Counselling for body weight reduction for patients with obesity is key within type 2 diabetes management guidelines.<sup>1 2</sup> The Look AHEAD trial showed weight reduction improved long-term glycaemic control over 4 years in patients with a median duration of 5 years of diabetes.<sup>3</sup> Similarly, Feldstein *et al*<sup>4</sup> in the USA, along with others,<sup>5</sup> found an association between initial weight loss with improved glycaemic and blood pressure control during the fourth year of follow-up in a cohort of 2574 newly diagnosed patients with type 2 diabetes, despite weight regain after initial weight loss. Authors have speculated that the initial period after diagnosis of type 2 diabetes may be critical for early

glycaemic control<sup>6</sup> and for applying weight loss interventions,<sup>4</sup> to improve glycaemia and risk factor control. Feldstein *et al*<sup>7</sup> findings also mirror those of the Finnish Diabetes Prevention Study and the Diabetes Prevention Program trials, where long-term prevention of diabetes was seen in the lifestyle intervention arms, again despite some weight regain.<sup>8 9</sup> While, the Look AHEAD and Finnish Diabetes Prevention trials were unable to demonstrate a reduction in cardiovascular events,<sup>10 11</sup> there have been some cost benefits seen especially for obese patients who lose weight.<sup>12</sup>

There is little information about variability of weight change in type 2 diabetes and the long-term outcomes. Zoppini *et al*<sup>13</sup> found an association between variability in body weight and glycaemic control over a 10-year follow-up period and saw increased mortality in older patients with type 2 diabetes. Weight change in people with diabetes may be unintentional and related to poor glycaemic control and the use of antihyperglycaemic treatment.<sup>14</sup> Thus, the main objective of this study is to investigate whether early changes after diagnosis in weight and glycaemic control, along with their variability, influence morbidity and mortality in type 2 diabetes, as well as treatment and glycaemic control.

## METHODS

In 2000, a population-based database, derived from primary and secondary care, was initiated as a register of people with diabetes across Scotland in the Scottish Care Information Diabetes Collaboration (SCI-DC) database<sup>15</sup> (SCI-Diabetes since 2012). This database contains demographic and clinical data covering over 99.5% of people with a diagnosis of diabetes in Scotland. A 2011 extract of the SCI-DC data set was linked to hospital admission, cancer registration and mortality records by the Information Services Division (ISD) of National Health Service (NHS) National Services Scotland. This data set and a retrospective cohort design approach was used to examine the main objectives.

## Study population

From the SCI-DC database, we extracted information on adult patients (>18 years) newly diagnosed with type 2 diabetes between 2002 and 2006. Patients with type 2 diabetes are a heterogeneous group; consequently we used rigorous inclusion/exclusion criteria (figure 1). People with a record of previous cancer, thyroid disease or on oral steroids were excluded. We selected these particular co-existing diseases from an otherwise numerous list as being the most likely for this patient group to promote weight loss. Excluded too were patients who had a body mass index (BMI) <25 kg/m<sup>2</sup> at diagnosis (ie, normal weight or less). Further, we excluded those who died or moved out of Scotland within the first 2 years after diagnosis (to reduce effects of illness-related weight loss), had a low glycated haemoglobin (HbA1c; <6.0%) at diagnosis or were prescribed insulin within 18 months of diagnosis

(to avoid including those more likely to have type 1 diabetes or who had had type 2 diabetes for a while prior to formal diagnosis). Given our interest in weight change patterns, those with only one recorded weight measure or with <21 months follow-up were also excluded. Successive records were examined and all data cleaned.

## Study variables

We used characteristic variables recorded at diagnosis, that is, gender, age, smoking status (unknown, current, ex, never) and deprivation, using the five-point Scottish Index of Multiple Deprivation (SIMD)<sup>16</sup> ranging from 'most deprived' to 'least deprived', the latter being our reference group. SIMD is an area-based measure which combines 38 indicators across seven domains, namely: income, employment, health, education, skills and training, housing, geographic access and crime. Ethnicity was not included in these analyses since this registry is primarily white European,<sup>17</sup> and while normally an important variable our focus was on weight change patterns.

Also included were successive measures of weight, BMI, drug treatment and HbA1c from diagnosis onwards to examine weight change and glycaemic control relationships. HbA1c was reported as percentages rather than in mmol/mol in the database. Where possible, we have given both. Record linkage allowed investigation of further relationships of these with subsequent all-cause mortality and cardiovascular outcomes (myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease and cerebrovascular disease identified using the International Classification of Diseases, 10th Edition (ICD-10) codes from hospital and death records).

## Baseline and follow-up epochs

Individuals' baseline was set as the date of weight recorded within  $\pm 3$  months of diagnosis. Similarly, the weight record closest to 12, 24, 36 and 60 months within a  $\pm 6$ -month window represented follow-up weight at 1, 2, 3 and 5 years, respectively. Pragmatically, the HbA1c measure recorded closest to the date of the selected weight record, within a  $\pm 3$ -month window, was matched to that weight. While the analyses were conducted on each of these epochs, this paper concentrates on the 2-year follow-up.

## Weight change and variation categories, and four weight change pattern groups

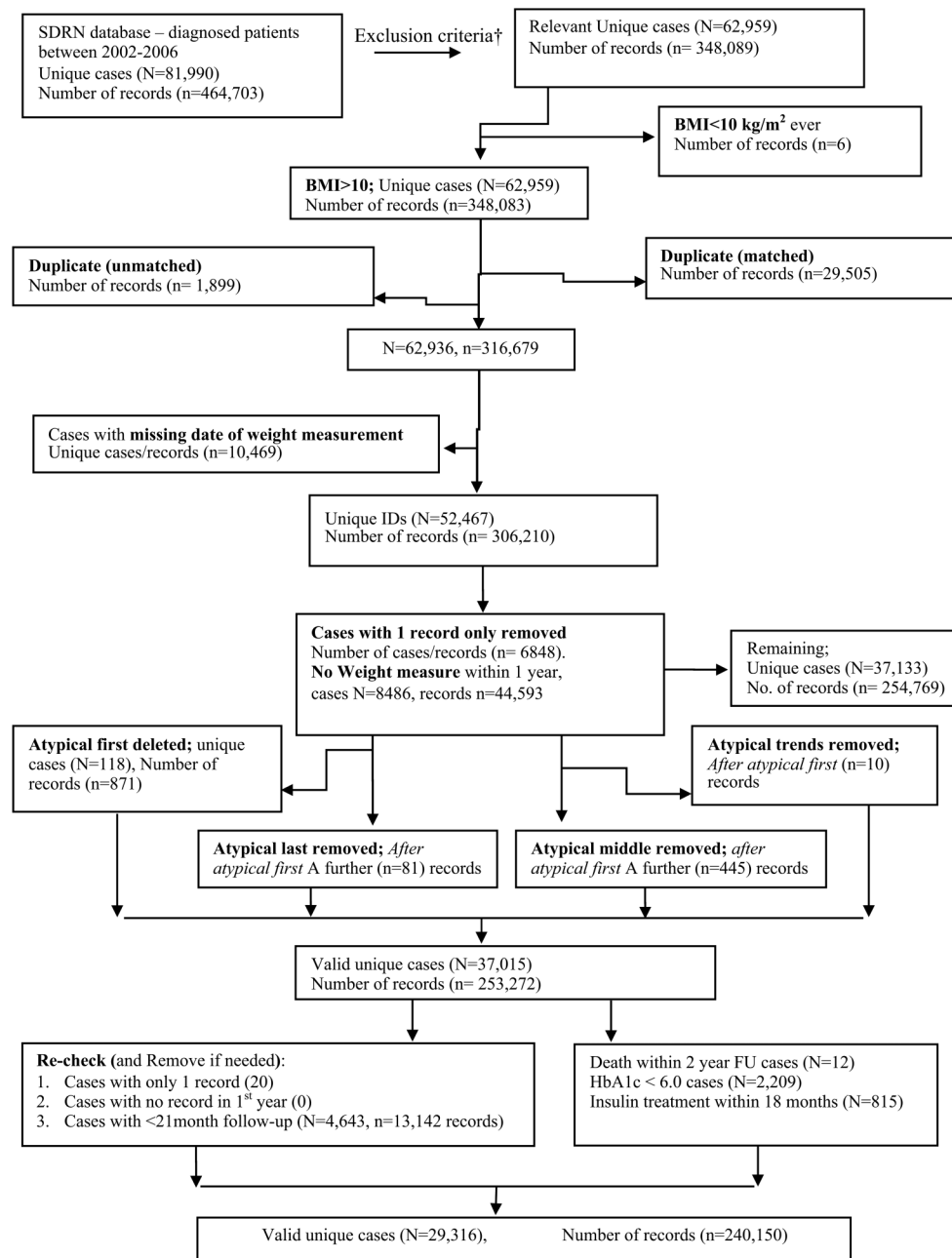
Percentage weight change was calculated overall and within each specified follow-up period (1, 2, 3 and 5 years) then categorised as follows:

*Loss:* 10% or more, <10% to 5%, <5% to 2.5%;

*Stable:* Loss of 2.5% up to gain of 2.5%;

*Gain:* >2.5% to 5%, >5% to 10%, 10% or more.

The weight stable group is based on the National Institute for Health and Care Excellence (NICE) Public Health Guidance no 53,<sup>18</sup> which indicates that a 3% long-term weight loss is associated with health benefits.



† Exclusion criteria: Those with cancer, thyroid disease, on oral steroids, or with a BMI less than 25 kg/m<sup>2</sup> at diagnosis

SDRN: Scottish Diabetes Research Network

‡ Atypical: Values within a person's record deemed to be clinically unlikely

**Figure 1** Summarising clinical and data cleaning exclusions. BMI, body mass index; FU, follow-up; HbA1c, glycated haemoglobin.

The coefficient of variation (cv) of weight change for each patient was calculated for the different follow-up periods to measure variability or cycling of weight, as follows:

$$cv = \frac{\text{standard deviation of weight (per patient)}}{\text{mean weight (per patient)}}$$

then given the skewness of the distribution of the number of visits (median=6; IQR 4–9)) this was categorised into:

*Little* (<2.5%),  
*Some* (2.5 to <5%),  
*Moderate* (5 to <10%) and  
*Large* (10%+).

While weight loss and gain are expected to be variable, variation in the weight stable group may be detrimental. Consequently this group was further divided into stable and steady over each follow-up period thus providing just four broad weight patterns: loss, stable-steady (little variation cv<2.5%), stable-cyclic (cv≥2.5%) and gain.



### Antidiabetic medication groupings

Medication needs considering when relating weight change and patterns of weight change to glycaemic control, since some glucose-lowering treatments induce weight gain or loss. While in practice many combinations of medication may be expected, we concentrated on specific groupings using a ladder approach based on drugs most likely to induce weight gain. Hence, within a follow-up period, a patient ever on insulin was grouped within the 'insulin combinations' group. The 'sulfonylurea (SU) combinations' group included anyone ever prescribed SUs during that time epoch but not insulin. Those on glitazones with or without metformin but not insulin or SU combinations were considered together, leaving those on metformin alone, and finally those on no antidiabetic drugs over the follow-up duration.

### Glycaemic control

Glycaemic control definitions vary. While  $<48$  mmol/mol (or 6.5%) is an absolute target, we defined 'control' as  $\text{HbA1c} \leq 53$  mmol/mol (or 7%), a commonly used clinical classification.<sup>5 6</sup>

### Statistical analyses

All analyses were conducted on SPSS V.23 and/or SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

Initially, characteristics of those included and excluded were compared. For the included patients, summary statistics for initial weight and HbA1c levels are investigated alongside patient characteristics. Associations of the derived weight change categories with initial patient characteristics were examined. Since not all participants had the same number of follow-up epochs, missing data were assessed and the baseline summaries were considered according to those in each epoch, although we concentrated on just the second year follow-up period. All the above basic comparisons used analysis of variance or independent t-tests, as appropriate. The progression of treatment combinations over time is graphically described, along with the relationship between the weight change categories (at 2 years) with initial HbA1c, and with the average changes seen in HbA1c, the latter also being split according to antidiabetic medication. Proportions of those in each of the four weight change patterns were also considered in relation to glycaemic 'control' having taken antidiabetic medication into account.

Relative risks (RRs) of glycaemic 'control' for the weight change groups were estimated using log-binomial regression models (since the proportion 'in control' vs 'not in control' was similar) except for non-converging models, where Poisson regression models with robust variance were used.<sup>19</sup> Weight change, weight variability, antidiabetic medication and weight change-medication interactions for each follow-up period were predictor variables, adjusted for patient characteristics at diagnosis, BMI, sex, smoking status and deprivation.

All-cause mortality is a single time event, while the cardiovascular outcomes are multiple events. For the latter, only the first event was analysed. Cox regression was conducted on deaths between 2 and 5 years (prior to 2 years were excluded to limit the potential for reverse causality from conditions that cause weight loss and increase mortality) and 0–5 years for cardiovascular first events (reverse causality is less of a concern for non-fatal cardiovascular events). These were modelled against: weight change, cv, antidiabetic medication and weight change-medication interactions, all at 2 years (considered to be a reasonable weight change assessment period); and adjusted for HbA1c control at 2 years, and patient characteristics at diagnosis, as given above. Those who had not died by the ISD extraction date were censored at that date (1 December 2013) as were those who had not experienced a cardiovascular event, unless the patient had died before, in which case the date of death was used as the cardiovascular event censored time.

Owing to the many analyses being performed and the larger sample sizes, significance levels were reduced to  $p < 0.001$  to assess the RRs for glycaemic control and the HRs for the cardiovascular outcomes.

## RESULTS

### Baseline characteristics

Originally 81 990 patients diagnosed with type 2 diabetes were recorded on the register between 2002 and 2006. After exclusions, the final sample had 29 316 cases with 240 150 records ([figure 1](#)). Excluded patients were slightly older (59.4 vs 58.4 years), more likely to be men (56.0% vs 54.4%), with a higher proportion with unknown smoking status (17.3% vs 12.7%), but fewer were classed as deprived using SIMD<sup>16</sup> categories: 46% in the two most deprived categories compared with 49.4% in the two least deprived categories. Although these were statistically significant, they were not considered clinically important (apart from smoking status), especially since the main aim was to investigate weight patterns and their potential effect.

For the included participants, the median (IQR) follow-up period was 5.2 years (3.8–6.2) with between 2 and 69 visits. At diagnosis for these patients ( $n=29\,316$ ), 54% were men, mean age was 58 years ( $SD=12$ ), mean HbA1c was 67 mmol/mol or 8.3% ( $SD=1.9$ ) and mean BMI was 33.2 ( $SD=6.0$ )  $\text{kg/m}^2$ . Men had slightly lower mean BMI (32.3,  $SD=5.3$ ) than women (34.2,  $SD=6.6$ ). [Table 1](#) shows younger patients and those most deprived to be clinically and statistically significantly heavier. Males were also statistically heavier than women but no more than expected given height differences. There were no differences in weight across the different smoking groups.

[Table 1](#) also shows that mean HbA1c at diagnosis ( $n=22\,781$ , not all included patients had an HbA1c measurement at diagnosis) was 66 mmol/mol or 8.2% ( $SD=1.9$ ). This differed between men and women and between age, smoking, deprivation and BMI groups.

**Table 1** Summary statistics of weight (kg) and HbA1c (%) at diagnosis by patient characteristics

Characteristics	Baseline weight (kg)				Baseline HbA1c (%)			
	Mean	SD	n	p Value*	Mean	SD	n	p Value*
Sex								
Male	97.7	18.0	15 955	<0.001	8.3	1.9	12 394	<0.001
Female	86.8	18.2	13 361		8.1	1.9	10 387	
Age group (years)								
<40	105.3	22.3	1793	<0.001	8.7	2.0	1436	<0.001
40–60	97.5	19.5	13 283		8.4	1.9	10 398	
≥60	86.7	15.6	14 240		8.0	1.9	10 947	
Smoking								
Unknown	92.9	19.2	3719	0.167	8.1	1.9	2806	<0.001
Current	92.5	18.7	6705		8.3	1.9	5252	
Ex-smoker	93.1	18.0	7817		8.1	1.9	6083	
Never smoked	92.5	19.5	11 075		8.2	1.9	8640	
Deprivation category†								
Most deprived	93.2	19.8	7380	<0.001	8.3	1.9	5808	<0.001
2	92.7	19.0	6917		8.2	1.9	5392	
3	93.2	18.8	5557		8.2	1.9	4271	
4	92.7	18.3	4905		8.2	1.9	3757	
Least deprived	91.4	17.8	4173		8.1	1.9	3252	
BMI category (kg/m <sup>2</sup> )								
25–29.9	78.3	10.0	10 153		8.3	2.1	7923	<0.001
30–34.9	91.0	11.4	10 120		8.2	1.9	7873	
35–39.9	102.9	13.0	5327		8.2	1.8	4135	
40+	122.3	18.8	3716		8.2	1.8	2850	
Total	92.7	18.9	29 316		8.2	1.9	22 781	
Patients with 2 years follow-up	92.5	18.7	20 856		8.2	1.9	16 225	

\*p Values are from ANOVA or independent t-test as appropriate.

†Categories of SIMD, <sup>16</sup> baseline weight n=28 932, baseline weight n=22 480.

ANOVA, analysis of variance; BMI, body mass index; HbA1c, glycated haemoglobin; SIMD, Scottish Index of Multiple Deprivation.

However, only age and BMI differences were of clinical importance: younger patients (<40 years) had higher mean baseline HbA1c level than older (≥60 years) patients (72 mmol/mol or 8.7%, SD=2.0 vs 64 mmol/mol or 8.0%, SD=1.9). Those who were overweight (≥25 BMI<30 kg/m<sup>2</sup>) had slightly higher mean baseline HbA1c (66 mmol/mol or 8.3%, SD=2.05) than those who were obese (BMI≥30 kg/m<sup>2</sup>) where it ranged between 65 and 66 mmol/mol or 8.1% and 8.2%.

### Missing data

Patient numbers fell with follow-up. However, patients still alive with relevant weight (n=20 856) and HbA1c (n=16 225) data after 2 years had similar diagnosis weight and HbA1c summary statistics (bottom line, table 1), thus still reflective of our original database. By 2 years, 29% and 37% of patients had missing data for weight (kg) and HbA1c, respectively (see online supplementary table S1). However, 99% of those with weight and HbA1c measures at 2 years also had information for the other variables of interest.

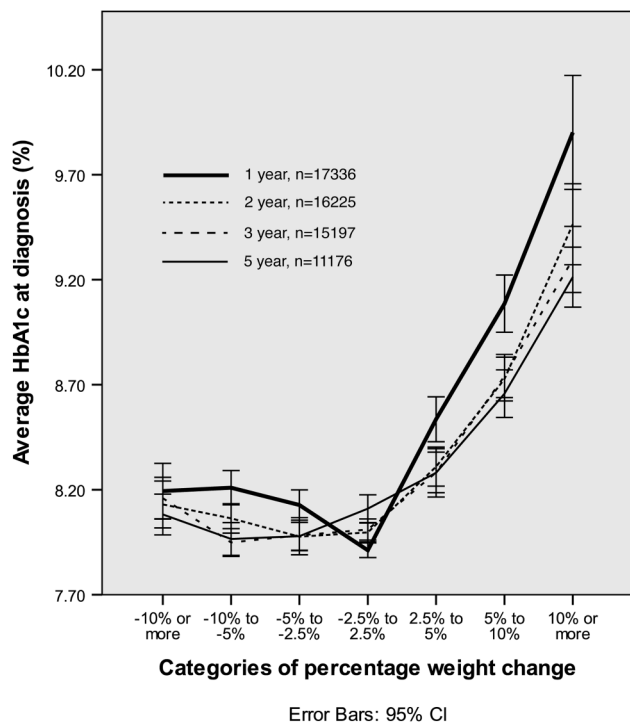
### Weight change

Of the 20 856 patients with 2-year follow-up data, the mean percentage weight change was small at  $-0.7\pm 6.7\%$ .

At a population level, BMI was also relatively unchanged, baseline mean BMI was 33.2 kg/m<sup>2</sup> (SD=6.0) at baseline and 32.8 kg/m<sup>2</sup> (SD=5.9) after 2 years. However, the percentage weight change categories over time show many were either weight stable or had weight loss: at 2 years, around 36% had lost weight (2.5% or more), with 21% losing more than 5% and 7% achieving 10% or more weight loss (see online supplementary figure S1a). These proportions were even higher after 5 years with 41% having weight loss, 28% with >5% weight loss and 11% with 10%+ weight loss. Variation of this weight change was, as expected, largest for those with the most weight change and increased with follow-up (see online supplementary figure S1b).

### Demographics associated with weight change

More women (40%) than men (32%) lost ≥2.5% of their body weight 2 years after diagnosis of diabetes with sex differences persisting even after 5 years (47% vs 35%, respectively). A larger per cent weight loss was significantly associated with higher BMI at diagnosis (see online supplementary table S2). Age at diagnosis was also significant with weight loss (mean age of those with 10% weight gain was 56 years (SD=12.6) compared with 59 years (SD=11.0) for those with 10% weight loss).



**Figure 2** Average HbA1c (%) at diagnosis with weight change for different follow-up periods (1, 2, 3 and 5 years). HbA1c, glycated haemoglobin.

#### Associations between weight change and HbA1c change

For each follow-up period, the mean HbA1c at diagnosis was lowest for those who lost weight or were weight stable. Conversely, diagnosis HbA1c was highest for those who later gained weight (figure 2).

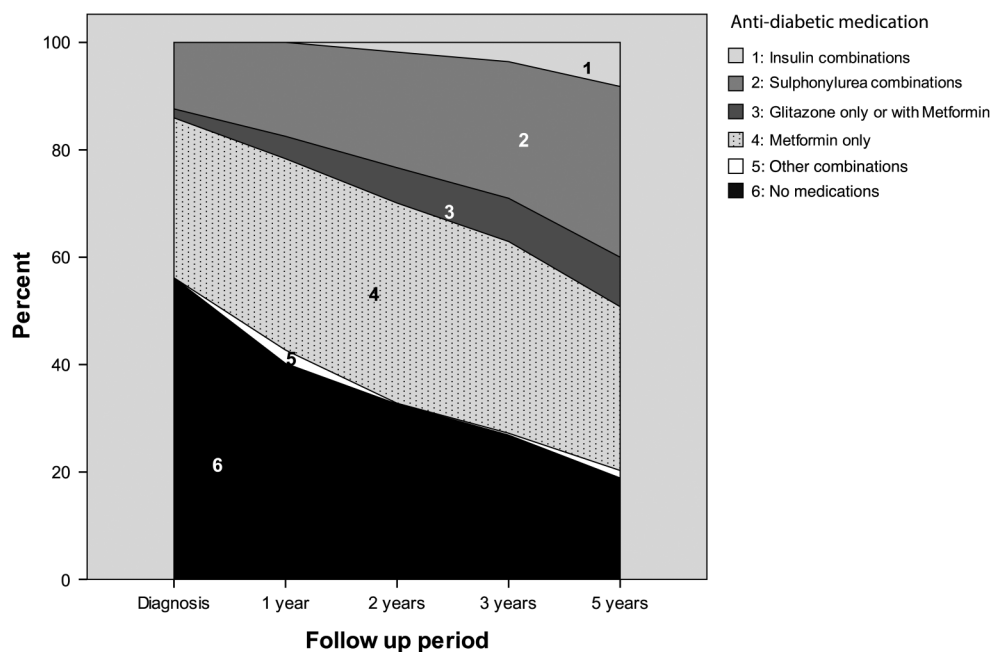
Next considered were patterns of weight change with glycaemic control in conjunction with the specified

antidiabetic medication groups. These groups accounted for 99.8% of all patients after 2 years. Figure 3 shows the proportions of these groups; those on no antidiabetic drugs initially represented around 56% of the sample declining to 19% by the fifth year. Metformin on its own was the most common drug with little variation for sole prescription (between 30% and 38%) over time, while the proportion of patients receiving any SU combination increased with time (12–32%). Glitazone prescription (with or without metformin) and insulin (with or without any other drug) also increased from virtually no prescriptions to around 10% after 5 years.

The mean HbA1c significantly dropped within the first year ( $p<0.001$ ) regardless of treatment but crept back up over time (table 2); online supplementary table S3 splits this for differing weight categories showing significantly that the mean HbA1c was lowest for those with 10% weight loss and largest for those with 10% weight gain regardless of follow-up time.

Figure 4 shows changes in HbA1c, 2 years after diagnosis of diabetes, by the different weight change categories and treatment groupings (associated sample sizes, see online supplementary table S4).

After 2 years, HbA1c reductions were associated with good weight loss and/or drug regimens. This pattern was similar for all follow-up periods (not shown). Patients with improved HbA1c levels tended to have weight loss or stability (78% after 1 year, 73% by the second year and 68% after 5 years) and were mostly on either metformin or no drugs (87% year 1, 73% years 2–5). Those on combinations of SUs or glitazones had greater improvement in HbA1c and also tended to gain weight. The exceptions were some patients on insulin, as seen in the top left of figure 4, who despite substantial



**Figure 3** Antidiabetic medication group proportions over follow-up.

**Table 2** Summary statistics of glycated haemoglobin (HbA1c) at baseline and then each time epoch

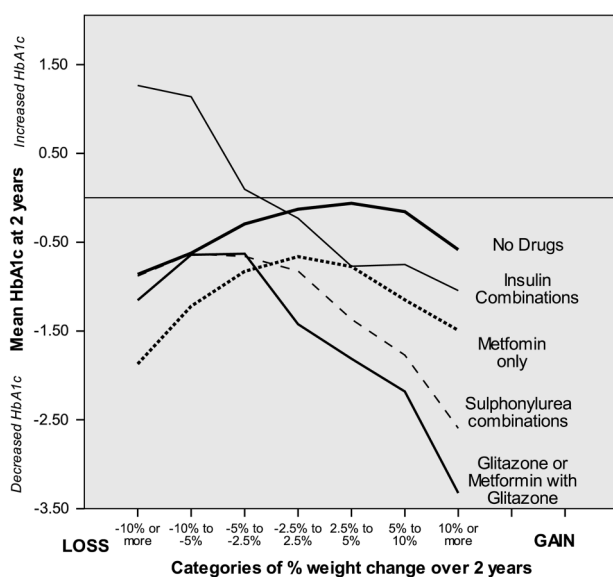
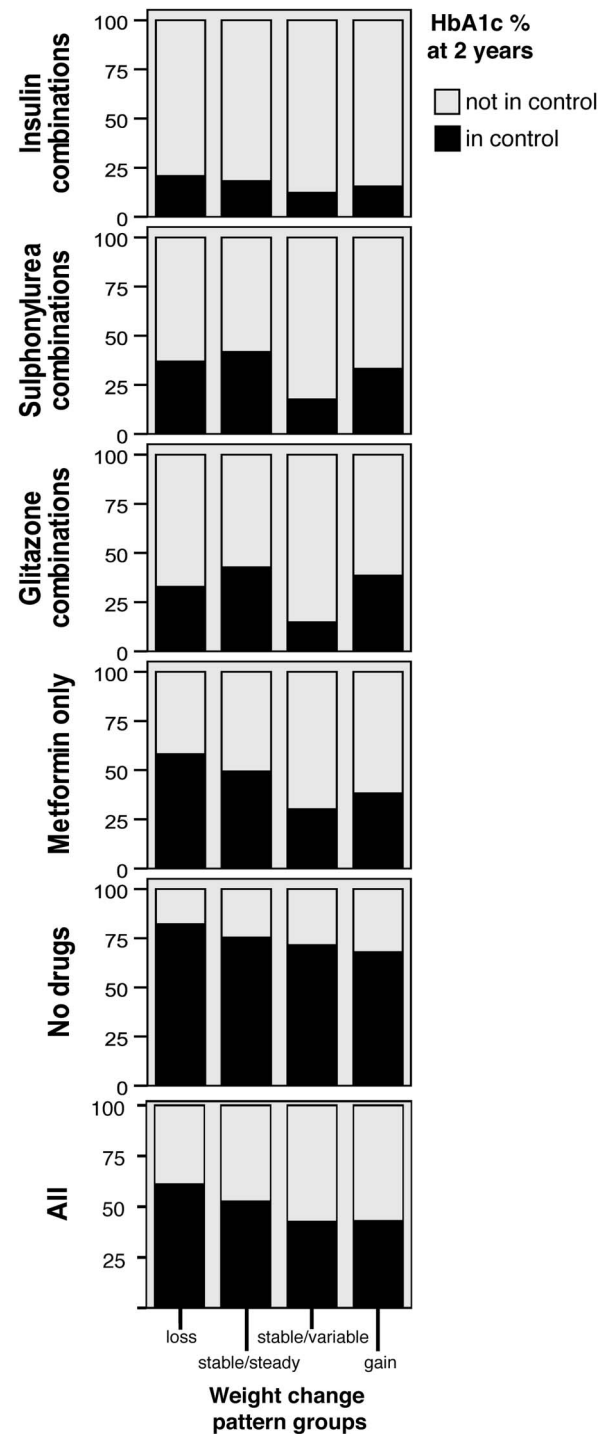
HbA1c per cent	N	Minimum	Maximum	Mean	SD
Baseline	22 781	6.00	18.00	8.19	1.93
After year 1	15 953	4.10	16.90	7.21	1.28
After year 2	18 591	4.10	17.00	7.33	1.36
After year 3	17 427	4.00	16.60	7.39	1.40
After year 5	12 644	4.10	16.60	7.49	1.50

weight loss (>5%) had increased HbA1c, possibly suggesting weight loss induced by poorly controlled diabetes.

The downward parabola-shaped response of HbA1c to per cent weight change (figure 4), except for those on insulin, also highlights the three broad bands of weight change (loss, stability and gain), giving rise to the investigation concentrating on 'weight loss' (more than 2.5% loss), 'weight stable' (between  $\pm 2.5\%$ ) and 'weight gain' (more than 2.5% gain).

Recall that the weight stable group was further divided to reflect variability into the 'weight stable-steady' and 'weight stable-cyclic' categories.

Using  $\text{HbA1c} \leq 7\%$  or 53 mmol/mol, as glycaemic control, we found that at diagnosis 36% were 'in control', improving to 55% within the first year, dropping to 51% for those after 2 years and levelling off to around 47% thereafter. Figure 5 illustrates this after 2 years, in conjunction with antiglycaemic medication and weight change pattern group. Greater proportions of people who lost weight, regardless of treatment, achieved glycaemic control at 2 years compared with those who gained or had stable weight.

**Figure 4** Mean HbA1c levels for each treatment combination and weight change category (at 2 years' follow-up). HbA1c, glycated haemoglobin.**Figure 5** Percentage of those in glycaemic control ( $\text{HbA1c} \leq 53$  mmol/mol (or 7%)) at 2 years' follow-up, by weight change pattern group and treatment. HbA1c, glycated haemoglobin.

Models for each follow-up period were derived using HbA1c 'in control'/'not in control' as a binary dependent variable. The four weight change patterns (loss, stable-steady, steady-cyclic and gain), the five variability cv categories and treatment combinations were included as predictors. In addition, an interactive term of weight change with treatment was included to accommodate



**Table 3** Multivariable RR for HbA1c>53 mmol/mol over specified follow-up periods (significance taken at p≤0.001)

Risk of HbA1c>53 mmol/mol (not in control) Variable	1-year follow-up Not in control n=7139			2-year follow-up Not in control n=8969			3-year follow-up Not in control n=8661			5-year follow-up Not in control n=6553		
	n	RR (95% CL)*	p Value	n	RR (95% CL)†	p Value	n	RR (95% CL)†	p Value	n	RR (95% CL)†	p Value
<b>AT diagnosis variables</b>												
Age	15 757	0.996 (0.995, 0.997)	<0.001	18 344	0.991 (0.990, 0.992)	<0.001	17 176	0.990 (0.988, 0.992)	<0.001	12 401	0.990 (0.988, 0.991)	<0.001
BMI, kg/m <sup>2</sup>												
30–34.9	5466	1.17 (1.09, 1.26)	<0.001	6336	1.13 (1.061, 1.20)	<0.001	5959	1.10 (1.03, 1.17)	0.003	4225	1.11 (1.04, 1.20)	0.003
35–39.9	2816	1.09 (1.04, 1.14)	<0.001	3311	1.07 (1.03, 1.11)	0.001	3084	1.05 (1.01, 1.09)	0.021	2224	1.06 (1.01, 1.11)	0.016
40+	1970	1.10 (1.05, 1.16)	<0.001	2233	1.06 (1.01, 1.11)	0.019	2145	1.06 (1.01, 1.11)	0.018	1578	1.06 (1.00, 1.11)	0.036
25–29.9 (ref)	5505	1		6464	1		5988	1		4374	1	
Sex												
Male	8483	0.98 (0.96, 1.02)	0.316	9949	1.01 (0.98, 1.04)	0.576	9301	1.02 (0.99, 1.05)	0.310	6795	1.05 (1.02, 1.09)	0.002
Female (ref)	7274	1		8395	1		7875	1		5606	1	
Smoking status at diagnosis												
Unknown	1940	1.05 (1.00, 1.10)	0.033	2353	0.95 (0.91, 0.99)	0.026	2153	0.97 (0.93, 1.02)	0.235	1423	0.99 (0.94, 1.04)	0.613
Current	3572	1.04 (1.01, 1.084)	0.025	4193	0.99 (0.95, 1.02)	0.392	3860	0.99 (0.95, 1.03)	0.532	2835	0.98 (0.94, 1.02)	0.278
Ex	4350	1.02 (0.99, 1.06)	0.291	4980	0.97 (0.94, 1.00)	0.086	4613	0.95 (0.92, 0.99)	0.019	3332	0.97 (0.94, 1.01)	0.193
Never (ref)	5895	1		6818	1		6550	1		4811	1	
Deprivation at diagnosis												
Most	3915	1.00 (0.95, 1.05)	0.999	4593	0.96 (0.91, 1.00)	0.050	4289	1.00 (0.95, 1.04)	0.883	3229	1.01 (0.96, 1.07)	0.717
2	3696	1.04 (0.99, 1.09)	0.173	4306	0.98 (0.94, 1.03)	0.461	4076	1.00 (0.95, 1.05)	0.992	2944	1.00 (0.95, 1.06)	0.884
3	2981	1.03 (0.98, 1.09)	0.222	3490	0.99 (0.94, 1.04)	0.652	3283	1.00 (0.96, 1.05)	0.907	2338	1.05 (1.00, 1.12)	0.062
4	2795	1.04 (0.98, 1.09)	0.218	3253	0.99 (0.94, 1.04)	0.670	2992	1.01 (0.96, 1.06)	0.659	2086	1.02 (0.96, 1.08)	0.511
Least (ref)	2370	1		2702	1		2536	1		1804	1	
<b>Time EPOCH variables</b>												
Anti-DM med groups												
Insulin Comb	0	–	–	329	4.06 (3.53, 4.67)	<0.001	635	4.28 (3.80, 4.82)	<0.001	1151	3.93 (3.39, 4.57)	<0.001
SU Comb	3050	2.97 (2.66, 3.31)	<0.001	4437	3.39 (3.06, 3.74)	<0.001	4933	3.21 (2.88, 3.57)	<0.001	4494	3.08 (2.67, 3.56)	<0.001
Glit Comb	738	3.54 (3.11, 4.03)	<0.001	1159	3.44 (3.04, 3.88)	<0.001	1361	2.95 (2.59, 3.36)	<0.001	1147	2.60 (2.19, 3.09)	<0.001
Met only	6003	2.18 (1.98, 2.41)	<0.001	6915	2.24 (2.03, 2.48)	<0.001	6247	2.11 (1.89, 2.35)	<0.001	3745	1.90 (1.64, 2.21)	<0.001
None (ref)	5966	1		5504	1		4000	1		1864	1	
Weight change												
S-S	3330	1.17 (1.01, 1.35)	0.031	3347	1.24 (1.07, 1.45)	0.005	1636	1.04 (0.86, 1.25)	0.694	1671	1.00 (0.73, 1.38)	0.982
S-C	3538	1.39 (1.23, 1.56)	<0.001	3535	1.43 (1.27, 1.62)	<0.001	2824	1.31 (1.13, 1.53)	<0.001	1768	1.44 (1.17, 1.78)	0.001
Gain	3538	1.75 (1.54, 1.97)	<0.001	4956	1.74 (1.54, 1.97)	<0.001	5076	1.62 (1.41, 1.86)	<0.001	3969	1.57 (1.28, 1.93)	<0.001
Loss (ref)	5466	1		6506	1		6414	1		4993	1	
CV												
2.5% to <5%	4686	0.88 (0.85, 0.92)	<0.001	6613	0.90 (0.87, 0.93)	<0.001	7074	0.91 (0.88, 0.94)	<0.001	5903	0.92 (0.89, 0.96)	<0.001
5% to <10%	1794	0.77 (0.72, 0.83)	<0.001	2532	0.77 (0.73, 0.81)	<0.001	2732	0.79 (0.75, 0.83)	<0.001	2564	0.80 (0.76, 0.84)	<0.001
10%+	321	0.68 (0.57, 0.80)	<0.001	392	0.64 (0.55, 0.73)	<0.001	441	0.65 (0.57, 0.73)	<0.001	382	0.74 (0.66, 0.83)	<0.001
<2.5% (ref)	8956	1		8807	1		6929	1		3552	1	

Continued

Table 3 Continued

Risk of HbA1c>53 mmol/mol (not in control) Variable	1-year follow-up Not in control n=7139			2-year follow-up Not in control n=8969			3-year follow-up Not in control n=8661			5-year follow-up Not in control n=6553		
	n	RR (95% CL)*	p Value	n	RR (95% CL)†	p Value	n	RR (95% CL)†	p Value	n	RR (95% CL)†	p Value
Anti-DM med/weight change interaction												
Insulin comb×S-S	0	–	–	41	0.76 (0.60, 0.97)	0.027	82	0.80 (0.64, 1.01)	0.058	121	0.89 (0.64, 1.25)	0.509
Insulin comb×S-C	0	–	–	48	0.74 (0.61, 0.90)	0.002	66	<b>0.73 (0.61, 0.87)</b>	<b>0.001</b>	128	0.77 (0.61, 0.96)	0.020
Insulin comb×gain	0	–	–	140	<b>0.62 (0.52, 0.74)</b>	<b>&lt;0.001</b>	317	<b>0.59 (0.50, 0.69)</b>	<b>&lt;0.001</b>	542	<b>0.69 (0.55, 0.85)</b>	<b>0.001</b>
SU comb×S-S	725	0.79 (0.67, 0.94)	0.007	891	<b>0.68 (0.58, 0.80)</b>	<b>&lt;0.001</b>	881	0.85 (0.70, 1.04)	0.105	684	0.94 (0.68, 1.30)	0.714
SU comb×S-C	493	0.89 (0.78, 1.02)	0.102	698	0.82 (0.70, 0.94)	0.005	710	0.87 (0.75, 1.02)	0.090	577	0.85 (0.68, 1.06)	0.148
SU comb×gain	1175	<b>0.66 (0.57, 0.76)</b>	<b>&lt;0.001</b>	1747	<b>0.62 (0.51, 0.71)</b>	<b>&lt;0.001</b>	1983	<b>0.65 (0.56, 0.75)</b>	<b>&lt;0.001</b>	1825	<b>0.71 (0.57, 0.87)</b>	<b>0.001</b>
Glit comb×S-S	189	0.74 (0.61, 0.90)	0.003	262	<b>0.63 (0.51, 0.77)</b>	<b>&lt;0.001</b>	260	0.79 (0.63, 1.00)	0.047	186	0.81 (0.56, 1.16)	0.247
Glit comb×S-C	127	0.81 (0.69, 0.95)	0.010	146	0.81 (0.69, 0.95)	0.012	163	0.87 (0.72, 1.05)	0.145	137	0.88 (0.69, 1.14)	0.342
Glit comb×gain	257	<b>0.53 (0.44, 0.64)</b>	<b>&lt;0.001</b>	483	<b>0.53 (0.45, 0.62)</b>	<b>&lt;0.001</b>	606	<b>0.59 (0.49, 0.70)</b>	<b>&lt;0.001</b>	518	<b>0.56 (0.44, 0.71)</b>	<b>&lt;0.001</b>
Met comb×S-S	1410	1.01 (0.87, 1.18)	0.856	1365	0.89 (0.75, 1.05)	0.150	1076	1.01 (0.82, 1.23)	0.959	487	1.10 (0.79, 1.54)	0.578
Met comb×S-C	1140	1.08 (0.95, 1.23)	0.223	1298	1.04 (0.91, 1.19)	0.540	1008	1.09 (0.93, 1.28)	0.540	548	1.05 (0.84, 1.32)	0.656
Met only×gain	1114	0.84 (0.73, 0.96)	0.013	1402	0.83 (0.72, 0.95)	0.006	1246	0.84 (0.72, 0.98)	0.006	684	1.01 (0.81, 1.25)	0.964
No anti-DM med	9127	1		9823	1		8778	1		5964	1	
and/or weight loss (ref)												
Constant		<b>0.37 (0.21, 0.28)</b>	<b>&lt;0.001</b>		<b>0.85 (0.30, 0.40)</b>	<b>&lt;0.001</b>		<b>0.71 (0.33, 0.44)</b>	<b>&lt;0.001</b>		<b>0.81 (0.32, 0.44)</b>	<b>&lt;0.001</b>

White background areas indicate significant increased risk of being 'out of control' at  $p \leq 0.001$  (to counter the large sample sizes).

Bold typeface indicates significant protective effect against being 'out of control' at  $p \leq 0.001$  (to counter the large sample sizes).

All predictors in the table are included as adjuster variables.

\*Binomial regression using generalised linear model with a log link.

†Poisson regression using generalised linear model with a log link (sandwich variance estimates) used if the binomial regression did not converge.

Anti-DM med, antidiabetic medication; BMI, body mass index; CL, confidence limit; comb, combinations (not including previous drugs in table); CV, coefficient of variation; Glit, glitazone or glitazone with metformin; HbA1c, glycated haemoglobin; Met, metformin; ref, reference group; RR, relative risk; S-C, weight stable/cyclic; S-S, weight stable/steady; SU, sulphonylurea.

**Table 4** Multivariable HRs for all-cause mortality and cardiovascular outcomes

HR for health outcome after 0–5 years	All-cause mortality 2–5 years 743 events n=17 711		MI 0–5 years 616 events n=18 236		CHF 0–5 years 425 cases n=18 192		PVD 0–5 years 300 events n=18 298		CD 0–5 years 360 events n=18 264	
	HR (95% CL)	p Value	HR (95% CL)	p Value	HR (95% CL)	p Value	HR (95% CL)	p Value	HR (95% CL)	p Value
Age at diagnosis	1.12 (1.11, 1.13)	<0.001	1.04 (1.03, 1.05)	<0.001	1.08 (1.06, 1.09)	<0.001	1.06 (1.04, 1.07)	<0.001	1.06 (1.05, 1.08)	<0.001
HbA1c 'not in control'	0.96 (0.82, 1.13)	0.632	1.09 (0.91, 1.29)	0.359	1.09 (0.88, 1.34)	0.428	1.01 (0.79, 1.30)	0.952	1.05 (0.84, 1.32)	0.654
At 2 years 'in control'* (ref)	1		1		1		1		1	
BMI at diagnosis, kg/m <sup>2</sup>		0.013				<0.001		0.558		0.044
30–34.9	0.94 (0.79, 1.11)	0.455	1.00 (0.83, 1.21)	0.966	1.14 (0.91, 1.44)	0.259	0.93 (0.72, 1.20)	0.577	0.97 (0.77, 1.23)	0.810
35–39.9	1.09 (0.87, 1.36)	0.456	1.21 (0.96, 1.52)	0.106	1.57 (1.19, 2.08)	0.002	0.83 (0.58, 1.20)	0.325	1.07 (0.79, 1.46)	0.643
40+	1.47 (1.12, 1.93)	0.005	0.85 (0.61, 1.19)	0.348	2.17 (1.55, 3.02)	<0.001	0.73 (0.44, 1.21)	0.219	0.49 (0.29, 0.83)	0.008
25–29.9 (ref)	1		1		1		1		1	
Sex, male	1.607 (1.37, 1.86)	<0.001	2.26 (1.89, 2.69)	<0.001	2.21 (1.79, 2.72)	<0.001	1.85 (1.44, 2.37)	<0.001	1.36 (1.09, 1.69)	0.006
Smoking status at diagnosis		<0.001		<0.001		0.001		<0.001		0.271
Unknown	1.50 (1.19, 1.90)	0.001	1.56 (1.18, 2.06)	0.002	1.40 (1.02, 1.932)	0.040	2.57 (1.64, 4.02)	<0.001	1.10 (0.78, 1.55)	0.589
Current	1.75 (1.43, 2.16)	<0.001	2.04 (1.64, 2.56)	<0.001	1.44 (1.08, 1.90)	0.012	5.23 (3.64, 7.52)	<0.001	1.33 (1.00, 1.77)	0.050
Ex-smoker	1.43 (1.19, 1.73)	<0.001	1.71 (1.38, 2.11)	<0.001	1.63 (1.28, 2.08)	<0.001	2.95 (2.04, 4.25)	<0.001	1.16 (0.89, 1.50)	0.283
Never (ref)	1		1		1		1		1	
Deprivation at diagnosis		0.001		<0.001		0.001		0.083		0.403
Most deprived	1.78 (1.35, 2.34)	<0.001	1.75 (1.31, 2.34)	<0.001	1.73 (1.17, 2.55)	0.006	1.06 (0.74, 1.53)	0.738	1.44 (1.00, 2.07)	0.052
2	1.59 (1.20, 2.09)	0.001	1.55 (1.15, 2.08)	0.003	1.81 (1.23, 2.66)	0.003	0.71 (0.48, 1.05)	0.087	1.22 (0.84, 1.77)	0.290
3	1.57 (1.19, 2.09)	0.002	1.26 (0.93, 1.73)	0.142	2.24 (1.52, 3.30)	<0.001	0.76 (0.50, 1.13)	0.174	1.24 (0.85, 1.83)	0.271
4	1.38 (1.02, 1.85)	0.035	1.154 (0.83, 1.59)	0.400	1.51 (1.00, 2.28)	0.052	0.82 (0.55, 1.24)	0.347	1.21 (0.82, 1.80)	0.337
Least deprived (ref)	1		1		1		1		1	
Anti-DM med groups (2 years)		<0.001		<0.001		<0.001		<0.001		0.002
Insulin comb	3.41 (1.71, 6.78)	<0.001	4.14 (2.24, 8.04)	<0.001	5.51(2.59, 11.72)	<0.001	5.12(1.97, 13.30)	0.001	4.83(1.88, 12.39)	0.001
Sulphonylurea comb	1.81 (1.33, 2.45)	<0.001	1.59 (1.13, 2.26)	0.009	2.03 (1.36, 3.04)	0.001	2.21 (1.33, 3.6)	0.002	2.01 (1.25, 3.24)	0.004
Glitazone comb	1.38 (0.74, 2.57)	0.317	1.02 (0.49, 2.12)	0.965	1.01 (0.40, 2.53)	0.990	0.33 (0.05, 2.40)	0.272	1.93 (0.81, 4.60)	0.137
Metformin only	1.03 (0.79, 1.33)	0.846	0.93 (0.68, 1.26)	0.620	0.92 (0.63, 1.33)	0.640	1.00 (0.63, 1.60)	0.998	1.20 (0.79, 1.82)	0.406
No drugs (ref)	1		1		1		1		1	
Weight change (2 years)		0.731		0.627		0.961		0.173		1.00
Stable-steady	0.86 (0.55, 1.33)	0.485	0.98 (0.62, 1.54)	0.931	0.97 (0.54, 1.77)	0.931	1.61 (0.87, 2.98)	0.132	0.97 (0.50, 1.89)	0.939
Stable-cyclic	0.83 (0.57, 1.19)	0.304	0.76 (0.50, 1.16)	0.201	0.86 (0.51, 1.47)	0.591	0.77 (0.40, 1.50)	0.439	1.00 (0.57, 1.74)	0.998
Gain	0.98 (0.69, 1.37)	0.888	0.94 (0.64, 1.39)	0.768	0.96 (0.59, 1.55)	0.861	0.81 (0.43, 1.55)	0.527	0.99 (0.57, 1.71)	0.963
Loss (ref)	1		1		1		1		1	

Continued

Table 4 Continued

HR for health outcome after 0–5 years	All-cause mortality		MI		CHF		PVD		CD	
	2–5 years 743 events n=17 711	HR (95% CL)	p Value	0–5 years 616 events n=18 236	HR (95% CL)	p Value	0–5 years 300 events n=18 298	HR (95% CL)	p Value	0–5 years 360 events n=18 264
CV of weight change (2 years)			<0.001			0.004			<0.001	0.315
2.5% to <5%		1.14 (0.94, 1.38)	0.182		1.15 (0.94, 1.41)	0.189		1.21 (0.90, 1.63)	0.208	1.23 (0.94, 1.60)
5% to <10%		1.77 (1.41, 2.23)	<0.001		1.57 (1.21, 2.03)	<0.001		1.55 (1.07, 2.24)	0.021	1.36 (0.96, 1.92)
10%+		2.49 (1.68, 3.68)	<0.001		0.99 (0.54, 1.84)	0.976		2.08 (1.06, 4.08)	0.034	1.11 (0.51, 2.42)
<2.5% (ref)		1			1			1		1
Anti-DM med/weight change interaction (details not given)			0.583			0.914			0.360	0.929

White background areas indicate significant increased risk ( $p \leq 0.001$ ).

All predictors in the table are included as adjuster variables.

\*HbA1c &lt; 53 mmol/mol.

Anti-DM med, antidiabetic medication; BMI, body mass index; CD, cerebrovascular disease; CHF, congestive heart failure; CL, confidence limit; comb, combinations (not including previous drugs in table); CV, coefficient of variation; MI, myocardial infarction; PVD, peripheral vascular disease; ref, reference group.

potential confounding of treatment on weight change. All models were adjusted for characteristics at diagnosis (age, BMI, sex, smoking status and deprivation), variables known to potentially effect HbA1c and change in weight. Table 3 presents RRs for all follow-up periods. Generally younger patients and/or those with higher baseline BMI had increased risk of 'not being in control' later. Sex, smoking status and deprivation were generally not significant factors. However, being on anti-diabetic medication was associated with being 'not in control' (eg, those on insulin at 2 years were four times more likely to have higher HbA1c and have weight gain). Compared with weight loss or even stable-steady, the weight gain and stable-cyclic groups were more likely to have higher HbA1c levels. However, larger weight variations were more related to HbA1c being 'in control'. There were also positive associations for better HbA1c control with the drug-weight change interactions (gain with SU or glitazone combinations) compared with the weight loss or not on drugs groups.

Table 4 gives the hazard rates for all-cause mortality and the different cardiovascular outcomes (MI, CHF, peripheral vascular disease and cerebrovascular disease) adjusted for patient characteristics, weight change patterns and antidiabetic medication regimes. It shows similar risk factors across the different health outcomes. All were associated with increasing age, being male (except cerebrovascular disease), smoking (even ex-smokers, although not for cerebrovascular disease) and increased deprivation (not for peripheral vascular disease and cerebrovascular disease). Morbid obesity ( $\text{BMI} \geq 40$ ) at diagnosis was associated with higher risks for mortality and CHF than being overweight ( $\text{BMI} 25\text{--}29.9$ ).

Across all outcomes, insulin combinations were 3–5 times associated with increased mortality risk compared with the no drug group, while SU combinations had even greater associations with mortality and CHF. Although included, good glycaemic control at 2 years was not significant with respect to these later health outcomes. Weight change itself was not statistically associated, but weight variability was a significant risk factor related to mortality, and to a lesser extent for MI and CHF. Drug-weight interactions were investigated, but none were statistically significant (only overall p values are given).

## DISCUSSION

This study examined weight change patterns in a large contemporary cohort of overweight or obese patients newly diagnosed with type 2 diabetes. The weight loss benefits on glycaemic control and decreased need for antihyperglycaemic therapy are well documented,<sup>12 20</sup> along with reduced disability risks.<sup>5</sup> The national Scottish guidelines recommend that obese adults with type 2 diabetes should be offered individualised interventions to encourage weight loss.<sup>21</sup> While we found the mean percentage weight change after 2 years was only



$-0.7\pm 6.7\%$  (persisting up to 5 years), a subgroup (36%) had lost weight by 2 years with 59.2% of them losing more than 5%; the corresponding figures by 5 years were 41% and 68%, respectively. Women were more likely to lose 5% or more weight than men over the 5 years. Older people (60 years+) and people with higher initial BMIs were also more likely to lose weight. This weight lost suggests real effort from this subgroup, especially since some diabetic treatments induce weight gain; moreover weight tends to increase over time in the general population.<sup>22</sup> Morgan *et al*<sup>23</sup> showed weight increases over 1995–2010 for those first diagnosed with type 2 diabetes.

In this cohort, those younger at diagnosis were significantly more obese with higher HbA1c levels. However, around 36% of the entire cohort had 'in control' HbA1c levels ( $\leq 7\%$  or 53 mmol/mol) at diagnosis, increasing to 47% after 5 years. This was more likely for patients with significant weight loss or the weight stable-steady group, irrespective of antihyperglycaemic medication. By 2 and 5 years, 13% and 8%, respectively, had good glycaemic control (HbA1c $<6.5\%$  or 48 mmol/mol) without diabetic medication. Mean HbA1c was lowest for those with 10% weight loss and highest for those with 10% weight gain. Best glycaemic control was associated with metformin, particularly if with weight loss. de Fine Olivarius *et al*<sup>24</sup> also found weight loss common for diabetics within 5 years of diagnosis, but did not find weight affected by SU treatment combinations. In contrast, we found insulin, SU and glitazone combinations all to be associated with weight gain, albeit with better glycaemic control. What cannot be determined is the casual path of these factors.

Factors associated with poor control (HbA1c $>7\%$  or 53 mmol/mol) at 5 years included being younger, having a higher diagnosis BMI and to a lesser extent being female and/or deprived. Perhaps contradictory are the coefficient of variation results where large weight variation was associated with better glycaemic control. However, the direction of the weight change is indistinguishable here. 'Control' was associated with progressive weight loss and also with weight gain when combined with antidiabetic medication. The better glycaemic control seen for the interaction between diabetic medication and weight gain may also be due to medication rather than increased weight. Other explanatory factors include differences in lifestyle, medication adherence, response to medication or the propensity for side effects.<sup>25 26</sup>

Higher mortality and cardiac failure after 2 years were also associated with severe obesity (BMI $\geq 40$ ) at diagnosis (table 4). HbA1c control at 2 years was not related to any of these outcomes, perhaps because glycaemic control often includes insulin and SU use, themselves associated with adverse prognosis and confounding the results. Weight change at 2 years was also not significantly associated with these outcomes. However, weight variability was significant, with mortality risk for the

weight stable-cyclic group being double that of the weight loss group. Similar associations were seen for MI and cardiac failure. Weight variability may reflect other illnesses, themselves associated with poorer outcomes. What cannot be determined from these data is if weight change was intentional. It is known that unintentional weight loss is often the result of illness.<sup>14</sup> While we have excluded those who died within the first 2 years, we cannot exclude significant comorbidity that might be contributing to the variability.

This study may be limited by the observational nature of the data. However, access to such a large community-based population is rare and provides detailed investigative opportunities. While the proportion of data exclusions seems large, this is common for routinely collected data often subject to incomplete data or input errors. Reassuringly, the characteristics of patients satisfying the per-protocol inclusion criteria were compared with those subsequently excluded for data cleaning reasons, with no clinically important differences. Further, the characteristics of this selected cohort after data cleaning and clinical exclusions are consistent with previous characterisation from the SCI-DC registry<sup>14</sup> suggesting they reflect the general diabetic population in Scotland.

It was difficult to separate the effects of glycaemic control, treatment and weight change.<sup>23</sup> While 30% had no glucose-lowering drugs after 2 years, this was only 19% after 5 years. Sinclair *et al*<sup>27</sup> noted that only 51% of patients in their study had antihyperglycaemic medication within 2 years of diagnosis. These treatments are generally associated with weight loss (eg, metformin) or gain (eg, insulin, SUs, glitazones) seen here and elsewhere.<sup>28</sup> Unfortunately, our cohort did not include patients on the newer treatments in sufficient numbers suitable for analysis, for example, glucagon-like peptide-1 receptor agonists, gliptins. We also did not examine the effect of blood pressure and lipids along with their associated treatment regimens. Obesity was measured by BMI, since other variables like waist circumference were not available.

In line with other studies, we found encouraging relationships between long-term weight loss, better glycaemic control and less antidiabetic medication. Feldstein *et al*<sup>7</sup> in their small US study, speculated that the initial period after diagnosis of type 2 diabetes may be critical for weight loss interventions to improve glycaemia and risk factor control, based on a retrospective cohort—those with weight loss in the first 18 months, even with regain, had better glycaemic and blood pressure control in the second 18 months. Conversely, Fumelli *et al*<sup>29</sup> in Italy did not find BMI change and HbA1c associations over 3 years. However, this was a small, poor quality study. Like our study, the US study<sup>4</sup> found women and older people more likely to achieve weight loss, with our research highlighting the need to better support some patients less likely to do well. Janghorbani *et al*<sup>30</sup> examined predictors of weight change in type 2 diabetes in an Iranian population over

9 years. While they did not find BMI > 40 predicted greater weight loss, they did agree with our findings that women were more likely to lose the most weight, and insulin is likely to be associated with poor glycaemic control and weight loss. Another paper by Janghorbani *et al*<sup>31</sup> found that insulin tended to improve HbA1c with weight gain, possibly related to better glycaemic control. The impact of weight loss on mortality in type 2 diabetes is a subject of debate. Here we saw weight loss benefits and increased mortality risks with large weight change variability. A review of six published observational studies showed divergent results on the topic with one study showing no association between weight loss and longevity, two associated weight loss with decreased mortality, one with increased mortality and two reported varying mortality outcomes in different subgroups.<sup>32</sup> In a smaller older cohort, poorer glycaemic control at diagnosis adversely affected survival, but weight loss in the first year was associated with improved survival.<sup>33</sup> Logue *et al*,<sup>34</sup> using an earlier cross-sectional study in same diabetes register database used here, found the highest mortality for those with BMI ≥ 35, and increasing vascular mortality BMI ≥ 30, but did not examine weight change. Carnethon *et al*<sup>35</sup> found that type 2 diabetics with BMI < 25 at diagnosis had the highest total and non-cardiovascular mortality, but was a relatively small under-powered study and may instead reflect differing genetic predisposition to diabetes and other underlying illnesses, a group we excluded because of the higher chance of misdiagnosis. Our focus was on weight change patterns, but this apparent adverse effect of SUs and other antidiabetic medications on mortality has been described elsewhere including metformin, as discussed by Roumie *et al*.<sup>36</sup>

To date, weight cycling has been alluded to as being important but without there being any standard definitions or consistency of results. Mehta *et al*<sup>37</sup> recently undertook a systematic review of the impact of weight cycling on the risk of morbidity and mortality finding limited evidence to support any adverse effects of weight cycling. One US study by Arnold *et al*<sup>38</sup> found an association between weight variability/cycling with physical functioning and mortality in an older group of individuals but not all had type 2 diabetes. Our study investigated this in more detail for patients with diabetes and suggests that weight cycling is generally detrimental for those who are overall weight stable.

Our results show that substantial weight loss is achieved by a significant proportion of patients receiving standard care within Scotland. We highlight the significance of weight loss on improving HbA1c, thus indicating the importance of diabetes services in promoting intentional weight loss after diagnosis of type 2 diabetes. One such trial actively testing this is now in progress.<sup>39</sup> Provision for maintenance strategies are also needed since weight stability with notable weight variability may be detrimental. Further, we have identified specific target groups who would benefit from access to more structured

interventions for weight loss, these being younger patients with higher BMIs, and also men and those from more deprived communities. Within Scotland, there is now a process to review patient education programmes and whether they meet structured education criteria.<sup>40</sup> Our results should be considered within such processes.

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#### REFERENCES

1. SIGN. Scottish Intercollegiate Guidelines Network. Management of diabetes. A national clinical guideline. 115. Edinburgh, Scottish

- Intercollegiate Guidelines Network. 2010. <http://www.sign.ac.uk/pdf/sign115.pdf> (accessed 06 Apr 2016).
2. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55:1577–96.
3. Wing RR, Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170:1566–75.
4. Feldstein AC, Nichols GA, Smith DH, *et al.* Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care* 2008;31:1960–5.
5. Chiu CJ, Wray LA, Lu FH, *et al.* BMI change patterns and disability development of middle-aged adults with diabetes: a dual trajectory modeling approach. *J Gen Intern Med* 2013;28:1150–6.
6. Berkowitz SA, Krumme AA, Avorn J, *et al.* Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study. *JAMA Intern Med* 2014;174:1955–62.
7. Feldstein AC, Nichols GA, Smith DH, *et al.* Weight change and glycemic control after diagnosis of type 2 diabetes. *J Gen Intern Med* 2008;23:1339–45.
8. Lindström J, Ilanne-Parikka P, Peltonen M, *et al.* Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–9.
9. Knowler WC, Fowler SE, Hamman RF, *et al.*, Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677–86.
10. Wing RR, Bolin P, Brancati FL, *et al.*, Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–54.
11. Uusitupa M, Peltonen, Lindstrom J, *et al.* Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study—secondary analysis of the randomized trial. *PLoS ONE* 2009;4:e5656.
12. Yu AP, Wu EQ, Birnbaum HG, *et al.* Short-term economic impact of body weight change among patients with type 2 diabetes treated with antidiabetic agents: analysis using claims, laboratory, and medical record data. *Curr Med Res Opin* 2007;23:2157–69.
13. Zoppini G, Verlato G, Targher G, *et al.* Variability of body weight, pulse pressure and glycaemia strongly predict total mortality in elderly type 2 diabetic patients. The Verona Diabetes Study. *Diabetes Metab Res Rev* 2008;24:624–8.
14. Pi-Sunyer FX. Weight and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 1996;63:426S–9S.
15. SCI-DC. Scottish Care Information—Diabetes Collaboration. 2013. <http://www.sci-diabetes.scot.nhs.uk/> (accessed 06 Apr 2016).
16. The Scottish Government. Scottish index of multiple deprivation 2012: A National Statistics Publication for Scotland. 28-8-2012. Edinburgh. [http://22fa0f74501b902c9f11-8b3fbdffa1e1fab453a8e75cb14f3396.r26.cf3.rackcdn.com/simd\\_448749\\_v7\\_20121217.pdf](http://22fa0f74501b902c9f11-8b3fbdffa1e1fab453a8e75cb14f3396.r26.cf3.rackcdn.com/simd_448749_v7_20121217.pdf) (accessed 06 Apr 2016).
17. Negandhi PH, Ghouri N, Colhoun HM, *et al.* Ethnic differences in glycaemic control in people with type 2 diabetes mellitus living in Scotland. *PLoS ONE* 2013;8:e83292.
18. NICE. Weight management: lifestyle services for overweight or obese adults: Nice guideline [PH 53]. PH53. 2014. <https://www.nice.org.uk/guidance/ph53/resources/weight-management-lifestyle-services-for-overweight-or-obese-adults-1996416726469> (accessed 06 Apr 2016).
19. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol* 2005;162:199–200.
20. Wilding JPH. The importance of weight management in type 2 diabetes mellitus. *Int J Clin Pract* 2013;68:682–91.
21. SIGN. Scottish Intercollegiate Guidelines Network. Management of Diabetes. 116. 2010. Edinburgh, Scottish Intercollegiate Guidelines Network. <http://www.sign.ac.uk/pdf/sign116.pdf> (accessed 06 Apr 2016).
22. Moody A. Health and Social Care Information Centre. Health Survey for England—2013. Vol 1 Chapter 10 Adult anthropometric measures, overweight and obesity. 2013. <http://www.hscic.gov.uk/catalogue/PUB16076/HSE2013-Ch10-Adult-anth-meas.pdf> (accessed 06 Apr 2016).
23. Morgan CL, Jenkins-Jones S, Evans M, *et al.* Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs. *Diabetes Obes Metab* 2012;14:424–32.
24. de Fine Olivarius N, Andreasen AH, Siersma V, *et al.* Changes in patient weight and the impact of antidiabetic therapy during the first 5 years after diagnosis of diabetes mellitus. *Diabetologia* 2006;49:2058–67.
25. Curkendall SM, Thomas N, Bell KF, *et al.* Predictors of medication adherence in patients with type 2 diabetes mellitus. *Curr Med Res Opin* 2013;29:1275–86.
26. Nam S, Chesla C, Stotts NA, *et al.* Barriers to diabetes management: patient and provider factors. *Diabetes Res Clin Pract* 2011;93:1–9.
27. Sinclair A, Alexander C, Davies M, *et al.* Factors associated with initiation of antihyperglycaemic medication in UK patients with newly diagnosed type 2 diabetes. *BMC Endocr Disord* 2012;12:1.
28. Aquilante CL. Sulfonylurea pharmacogenomics in Type 2 diabetes: the influence of drug target and diabetes risk polymorphisms. *Expert Rev Cardiovasc Ther* 2010;8:359–72.
29. Fumelli P, Boemi M, Romagnoli F, *et al.* Influence of body mass on glycemic control in a type 2 diabetic population: a 3-year follow-up. *Arch Gerontol Geriatr* 2000;30:1–5.
30. Janghorbani M, Amini M. Patterns and predictors of long-term weight change in patients with type 2 diabetes mellitus. *Ann Nutr Metab* 2009;54:111–18.
31. Janghorbani M, Amini M, Salehi-Marzjarani M. Weight change, blood pressure, lipids and glycemic control among patients with type 2 diabetes. *Ann Nutr Metab* 2011;58:141–9.
32. Williamson DF. Weight loss and mortality in persons with type-2 diabetes mellitus: a review of the epidemiological evidence. *Exp Clin Endocrinol Diabetes* 1998;106(Suppl 2):14–21.
33. Lean ME, Powrie JK, Anderson AS, *et al.* Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 1990;7:228–33.
34. Logue J, Walker JJ, Leese G, *et al.* Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care* 2013;36:887–93.
35. Carnethon MR, De Chavez PJ, Biggs ML, *et al.* Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012;308:581–90.
36. Roumie CL, Hung AM, Greevy RA, *et al.* Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2012;157:601–10.
37. Mehta T, Smith DL, Muhammad J, *et al.* Impact of weight cycling on risk of morbidity and mortality. *Obes Rev* 2014;15:870–81.
38. Arnold AM, Newman AB, Cushman M, *et al.* Body weight dynamics and their association with physical function and mortality in older adults: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci* 2010;65:63–70.
39. Lean ME. Reversal of T2DM to normal glucose tolerance using non-surgical weight management with low-energy-liquid-diet and long-term maintenance, within routine NHS care. Diabetes UK Research Award. 2014-2018. <https://www.diabetes.org.uk/Research/Our-research-projects/Scotland/The-DIRECT-route-to-Type-2-remission/> (accessed 06 Apr 2016).
40. McDowell J, MacRury S. Structured diabetes patient education in Scotland. *Pract Diabetes* 2015;32:24–8.

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# Patterns of weight change after the diagnosis of type 2 diabetes in Scotland and their relationship with glycaemic control, mortality and cardiovascular outcomes: a retrospective cohort study

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